

REMARKS

Claims 1-29 are pending in this application. Claims 10-29 have been withdrawn as being directed to a non-elected invention.

Claim 1 has been amended to recite the correct spelling of the word "proteins." No new matter has been added.

The Abstract has been amended to properly recite no more than 150 words and to delete the recitation of "(Fig. 7)." No new matter has been added.

Figure 8 has been deleted without prejudice or disclaimer. No new matter has been added.

The specification has been amended without prejudice or disclaimer, to delete reference to deleted Figure 8. No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At pages 1 and 2 of the Official Action, the Examiner objects to the Abstract, and to Figure 8.

The Examiner asserts that the Abstract should be on a separate sheet and should contain no more than 150 words. Accordingly, submitted herewith is a substitute sheet containing only the corrected abstract which includes not more than 150 words.

With regard to the sequence recitations in Figure 8, Applicants note this figure is a sequence comparison for illustrative purposes only. Accordingly, Figure 8 has been deleted without prejudice or disclaimer. Consistent therewith, the specification has been amended to delete any reference to Figure 8.

In view of the foregoing, the Examiner is respectfully requested to withdraw this objection.

II. At page 2 of the Official Action, the Examiner objects to claim 1.

The Examiner asserts that the word “proteins” is misspelled in line 3 of claim 1. Claim 1 has been amended to recite the correct spelling of the word “proteins.” Thus, the Examiner is respectfully requested to withdraw this objection.

III. At page 2 of the Official Action, claims 1 and 7-9 have been rejected under 35 USC § 112, second paragraph, as being indefinite.

The Examiner asserts the terms “conversion buffer” and “conversion temperature” appearing in claims 1 and 7-9, and in claim 1, respectively, are indefinite. The Examiner asserts that the terms are not defined by the claim and are not defined in the specification. The Examiner concludes that the skilled artisan would not be able to determine the metes and bounds of the invention.

In view of the remarks herein, this rejection is respectfully traversed.

The term “conversion” is used to indicate the suitability of the temperature and buffer selected to allow for a structural conversion when the other conditions set forth in steps a) to e) are met. Both terms must be considered in the context of the description as a whole. Hence, the skilled artisan will interpret the term “conversion” in the context of the present method for the conversion of one structural conformation into another. Reading the disclosure as a whole, the

skilled artisan would readily understand that the terms "conversion buffer" and "conversion temperature" mean "a buffer suitable for conversion" and "a temperature suitable for conversion," respectively. The skilled artisan can readily select temperatures and buffers without undue experimentation by evaluating the results of the present method, i.e., the formation of soluble lipid/amyloid protein complexes comprising soluble amyloid oligomers. Therefore, Applicants submit that the skilled artisan would fully understand the presently claimed subject matter.

In view of the foregoing, it is submitted that claims 1 and 7-9 are clear and definite within the meaning of 35 USC §112, second paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. At page 4 of the Official Action, claims 1 and 9 are rejected under 35 USC § 102 as anticipated by Martinez-Senac and Esler et al.

The Examiner asserts that Martinez-Senac teaches increased beta-sheet formation of amyloid peptide when interacting with negatively charged phospholipid vesicles. It is unclear how the Examiner relies on Esler et al. It is unclear whether the Examiner is rejecting claims 1 and 9 as anticipated by each of Martinez-Senac and Esler et al., or as obvious over the combination of Martinez-Senac and Esler et al. Accordingly, since the Examiner only addresses Martinez-Senac at pages 4-5 of the Official Action, Applicants' assume that the rejection of claims 1 and 9 as anticipated by Martinez-Senac was intended and thus, address that rejection.

In view of the remarks herein, this rejection is respectfully traversed.

Anticipation under 35 USC § 102 requires that a single prior art reference describe each and every element of the claimed invention. See *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

Applicant respectfully submits that Martinez-Senac does not teach each and every element of claims 1 and 9 as required for anticipation under 35 USC § 102.

Applicants note that Martinez-Senac actually discloses that negatively charged phospholipids greatly **accelerate the aggregation** of the specific amyloid peptide. In complete contrast, the method of claim 1 recites the use of negatively charged lipids for producing water soluble complexes of lamellar lipidic structures and conformationally transformed proteins, wherein the proteins have oligomeric beta-sheet intermediate structures. The proteins resulting for the method of claim 1 are soluble oligomers and are not insoluble aggregates. For the proteins resulting from the method of claim 1 to form aggregates, the complexes must be actively destroyed. These new, soluble and stable oligomeric amyloid complexes allow, for the first time, the study of the final step involved in amyloid aggregation and also permit the identification of inhibitors of the final aggregation.

Therefore, Applicants submit that Martinez-Senac does not teach a method for producing soluble lipid/amyloid protein complexes and does not teach producing oligomeric beta-sheet intermediate structures that are intermediate in that they have increased beta-sheet content but not yet enough to form amyloid aggregates, as claimed in present claim 1.

Accordingly, it is submitted that Martinez-Senac does not teach each and every element of present claims 1 and 9 as required for anticipation under 35 USC §102. Thus, the Examiner is respectfully requested to withdraw this rejection.

V. At page 6 of the Official Action, claims 1-9 have been rejected under 35 USC § 103(a) as being unpatentable over Martinez-Senac in view of Barrow et al. and Gursky et al. and Luhrs et al. and Pan et al. and Vold et al.

With regard to claims 2 and 3, the Examiner asserts that it would have been obvious to the skilled artisan to modify the method of Martinez-Senac by putting the vesicles in an environment such as pure water, that would destroy the micelles surrounding the amyloids to produce the insoluble amyloid fibrils as implied by Martinez-Senac and taught by Barow et al.

With regard to claims 4 and 5, the Examiner asserts that it would have been obvious to the skilled artisan to modify the method of Martinez-Senac by increasing the temperature once all components of the mixture were added as taught by Gursky et al.

Regarding claim 6, the Examiner asserts that it would have been obvious to modify the method of Martinez-Senac by utilizing a protein associated with Transmissible Spongiform Encephalopathy (TSE) as described in Luhrs et al. and Pan et al.

Lastly, regarding claims 7 and 8, the Examiner asserts that it would have been obvious to the skilled artisan to modify the method of Martinez-Senac by utilizing other phosphocholine family members such as DMPX and DHPC.

In view of the following, this rejection is respectfully traversed.

A brief outline of relevant authority, is set forth below.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04-1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost

of necessity will be combinations of what, in some sense, is already known.” (*KSR, supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Regarding motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations. Further, the Federal Circuit in *Takeda Chemical Industries v. Alphapharm*, No. 06-1329, slip op. (Fed. Cir. June 28, 2007), has **applied the TSM test after KSR**. The Appellant in this declaratory judgment action argued that the claimed chemical compound was an obvious modification of a previously known compound—the modification requiring the substitution of a homolog in a different ring position. (*Id.* at 5.) The Federal Circuit rejected this, holding that “in cases involving new chemical compounds, it remains necessary to identify some reasons that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.” (*Id.* at 10.) Notably, the Court also rejected the Appellant’s “obvious to try” argument, as the Appellant failed to

demonstrate that one of ordinary skill would have chosen the prior art compound to modify from the millions of possibilities. (*Id.* at 15.)

MPEP 2143.01 states that there are three possible sources for “a motivation” to combine references: the nature of the problem being solved; the teachings of the prior art; and the knowledge of one of ordinary skill in the art. Further, **MPEP 2145(X)(D)(2)** states that “It is improper to combine references where the references *teach away* from there combination.”

Regarding motivation to modify properly combined references, **MPEP 2143** states that where the prior art conflicts, all teachings must be considered and that the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. **MPEP 2143** further states that there must be some suggestion or motivation to modify the references, and there must be a reasonable expectation of success. In addition, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

MPEP 2143.01 states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, **MPEP 2141.02** states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also **MPEP 2145(X)(D)**.

It is submitted that a proper case of *prima facie* obviousness has not been established because there is no motivation to combine Martinez-Senac and Gursky et al. and because there is no motivation to modify Martinez-Senac by increasing the temperature once all components of the mixture were added as taught by Gursky et al.

Martinez-Senac describes the addition of negatively charged phospholipids to a specific amyloid peptide for increasing beta-sheet content and subsequent aggregation, i.e., precipitation.

Gursky et al. describes that once amyloids form beta sheets, this leads to insoluble amyloid fibrils. In particular, the passage at page 253, middle column, first paragraph, to the right column, first paragraph (as pointed out by the Examiner), makes it clear that pH changes can influence the rate of aggregation but not the result, i.e., insoluble precipitates.

Applicant's submit that there is no motivation to combine Martinez-Senac and Gursky et al. In fact, Martinez-Senac describes the accelerated aggregation of an amyloid protein in the presence of negatively charged lipids. Thus, there would be no reason to destroy the lipid vesicles because aggregation had already occurred.

Further, Gursky et al. also teaches the aggregation of amyloid proteins. Accordingly, there is no motivation to combine the teachings of Martinez-Senac and Gursky et al. because the result of both methods is essentially the same, i.e., precipitated amyloid aggregates.

Further, assuming *arguendo* motivation to combine, the presently claimed subject matter would not be produced. More specifically, neither Martinez-Senac nor Gursky et al., taken alone or together, suggest a method that results in obtaining a soluble and stable lipid/protein oligomer complex with increased beta-sheet content but not enough to aggregate.

With regard to claims 4-9, these claims are all directly or indirectly dependent on independent claim 1. Please see the arguments set forth above. It is submitted that none of Luhrs et al., Pan et al., and/or Vold et al. cure the deficiencies of Martinez-Senac and Gursky et al., because none of the secondary references suggest method that results in obtaining a soluble and stable lipid/protein oligomer complex with increased beta-sheet content but not enough to aggregate.

In view of the remarks set forth herein, it is submitted that nothing in any of the applied references, whether taken alone or in combination, render the subject matter of claim 1-9 obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Conclusion

In view of the foregoing, Applicant submits that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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